of the abdomen then takes place. This is obvious early in the x-ray films. If the enlarged loop does not respond to the deflating measures of intubation with a Harris tube or enemata and rectal tubes, suspicion of closed-loop obstruction should be aroused. In the case here reported the x-ray films, taken at ten-hour intervals, showed this quite well. They showed a gain in size of the closed-loop obstruction despite these measures. As a general rule, obstruction of the large bowel gives symptoms far less acute than does a high obstruction of the small bowel. However, when the large bowel obstruction is of the closed-loop variety, that is, a volvulus either of the ileocolic segment or of the sigmoid, the attendant symptoms are as rapid in onset and as severe in course as are those of upper small bowel obstruction. This too, then, is of diagnostic significance in volvulus of the large bowel.

It will be noted in the x-ray films that the dilated closed loop of obstructed bowel occupies the mid- and left lower quadrant of the abdomen, lying convexly to the left. This was borne out by the physical findings in the abdomen of the patient, the palpable mass lying transversely across the abdomen to the left. Because in by far the greater percentage of cases of volvulus of the cecum, the volvulus rotates in a clockwise direction to the left around the apex of the lowest portion of the fixed ascending colon, it is easy to see the reason for this. Volvulus of the sigmoid colon presents no such picture. The large dilated closed loop in this syndrome rises from the pelvis from a triangular terminal area and balloons into a loop which may occupy any portion of the lower abdomen, right or left. Volvulus of the terminal portion of the ileum, which accounts for about 47 per cent of all cases of intestinal volvulus as against 42 per cent for volvulus of the cecum and 11 per cent for volvulus of the sigmoid colon, may cause some diagnostic difficulty. In fact, one roentgenologist who was consulted in the case here reported, read the films as volvulus of the lower portion of the ileum. In such circumstances x-ray films should be of assistance if the haustral markings of the colon can be made out. In addition, the colon will usually show larger fluid levels present at an early stage of obstruction than will the small bowel.

490 Post Street.

REFERENCES

1. Rokitansky, C.: Intestinal strangulation, Arch. Gen. Med., 14:202, 1837.

2. Sweet, R. H.: Volvulus of the cecum, acute and chronic, New Eng. J. Med., 213:287, 1935.

Niemann-Pick's Disease and its Relationship to the Lipoidoses

RALPH E. KNUTTI, M.D., *Los Angeles*

THE group of lipoid diseases known as the xanthomatoses includes: (1) the primary type which is associated with cholesterosis, (2) the secondary type due to hyperlipemia, (3) the various types of xanthomatous deposits in tumors and inflammatory tissue, and (4) the metaplastic reticular and histiocytic diseases of Gaucher and Niemann-Pick which are associated with the specific lipoid materials kerasin and sphyngomyelin respectively. To these might be added the condition of familial amaurotic idiocy or Tay-Sach's disease. The term xanthomatosis is an unfortunate one to use in describing these diverse diseases. From its derivation it implies a yellow color such as that produced by cholesterol and bears no relationship to the various types of lipoids and lipochromes included under its heading. Pick himself[5] decried the term and suggested "lipoidosis" as a better one. Other authors[3, 8] feel that the term "xanthomatosis" should be restricted to those conditions in which cholesterol is the predominant lipoid. The lipoid nature of the chemical substances involved in the group is illustrated in Table 1.

The pathogenesis of Niemann-Pick's and Gaucher's diseases appears to be due to a disturbance of lipoid metabolism, the nature of which is controversial. Improved methods of chemical fractionation of lipoids in tissues have added much to knowledge of the subject. Gaucher felt that the disease bearing his name was a splenic neoplasm. Pick[4] suggested that hypercerebrosidemia with secondary storage of cerebrosides in the reticulum cells caused the condition, and he was the first proponent of the metabolic nature of this group of diseases. He also disagreed that Niemann-Pick's or Gaucher's disease represent lipoid histiocytosis. Thannhauser[7] and his associates elaborated the cellular theory,

From the Departments of Pathology, Children's Hospital, and the University of Southern California School of Medicine, Los Angeles.

Presented before the Section on Pediatrics at the 78th Annual Session of the California Medical Association, Los Angeles, May 8-11, 1949.

TABLE 1.—*Chemistry of Lipoidoses*

I. FATS: Glycerin + (Fatty acid, Fatty acid, Fatty acid)

II. LIPOIDS:

A. STEROLS

Cholesterol and its derivatives (Hand-Schuller-Christian)

B. PHOSPHATIDS

1. Glycerin + (Fatty acid, Fatty acid, PHOSPHORIC ACID+choline=LECITHIN or +ethanolamine=CEPHALIN)

2. Sphingosin + (Fatty acid, PHOSPHORIC ACID+choline=SPHINGOMYELIN (Niemann-Pick))

C. CEREBROSIDES

Sphingosin + (Fatty acid, GALACTOSE=KERASIN (Gaucher))

TABLE 2.—*Chemical Analyses in Niemann-Pick's and Tay-Sach's Diseases* (After Thannhauser)
Figures represent mg. per 100 cc.

	Spleen			Liver			Brain		
	Normal	Tay-Sach's	Niemann-Pick's	Normal	Tay-Sach's	Niemann-Pick's	Normal	Tay-Sach's	Niemann-Pick's
Total cholesterol	1.8- 2.4	3.10	6.73	2.0-2.6	3.78	7.0	7.3-15	9.90	6.45
Free cholesterol	1.6- 1.1	1.36	6.70	1.0-1.1	0.47	4.50	1.3-4.6	4.10	5.43
Cholesterol esters	0.7- 1.3	1.74	0.03	1.5-2.2	3.31	2.50	6.1-10.30	5.80	1.02
Total phospholipids	5.5-11.0	8.30	42.50	9.0-11.0	9.26	37.1	25-30	19.68	61.0
Sphyngomyelin	0.7- 1.0	1.04	32.70	0.3-0.5	0.55	25.90	4.5-7.0	7.04	4.84
Cephalin	1.5- 7.0	4.80		3.0-5.5	0		12-25		
Lecithin	3.0- 4.0	2.46		3.0-6.0	8.71		4.0-6.0		
Total fatty acids	4.0- 6.2	5.97		8.6-13.0	27.40				

namely, that the metabolic processes involved are within the cells. There is considerable evidence to support their conception of the pathogenesis of these diseases:

1. In Gaucher's disease kerasin is not increased in the serum.[6]

2. The kerasin present is found only within the reticular cells themselves.

3. An imbalance of the enzymes cerebrosidase and phosphorycholinesterase, normally present in cells, has been demonstrated,[9] and this imbalance is associated with the abnormal formation of sphyngomyelin or kerasin as the case may be.

Niemann-Pick's disease is the rarest of these conditions. Up to 1945, 60 cases[1, 2] had been reported. There were partial lipoid analyses in 12 of those cases, complete lipoid studies in nine. It is a disease of infancy, usually occurring in Jewish infants, is only slightly more frequent in females than in males[2] and terminates in death before the third birthday. In 15 of the 59 cases reviewed by Canmann[1] definite familial tendencies were shown. In common with other lipoid storage diseases, there is the characteristic occurrence of large abnormal lipoid-containing cells in various organs with enlargement of the liver and spleen. Clinically, it is frequently difficult to differentiate from Gaucher's disease. Other conditions which may confuse the diagnosis may be amaurotic familial idiocy (Tay-Sach's disease), von Gierke's disease, leukemia, and certain tumors of the liver (hepatoma, neuroblastoma). These latter conditions usually can be easily ruled out by clinical findings or suitable laboratory tests.

A case of Niemann-Pick's disease in the records of the Children's Hospital, Los Angeles, illustrates some of the factors involved in the clinical and pathological aspects of the lipoid storage diseases.

CASE HISTORY

A seven-month-old Jewish male was admitted to Children's Hospital with eczema of the face and scalp of three months' duration. He had been born after a full term pregnancy and normal labor. At birth an enlarged liver and spleen were noted but the patient was otherwise normal. Birth weight was 7 pounds 5 ounces. He was the second child of normal parents and had a four-year-old brother in good health. The feeding history and weight gain had been satisfactory, but at four months the child was unable to hold up its head. A raised, scaly patch developed on the left cheek, and gradually spread to the face and scalp. Therapy had been of no avail, and at seven months of age the patient was unable to hold up his head or sit up.

Physical examination revealed a well nourished infant who showed little reaction to objects brought near his face. There was an erythematous papular rash, eczematoid in nature, over the left cheek and scalp, with excoriations due to scratching. Questionable separation of the sutures of the skull was noted on palpation. No teeth were present. The heart was normal, but auscultation of the chest disclosed coarse wheezing rales bilaterally. The liver edge was palpable 4 to 5 cm. below the right costal margin, and the spleen was palpable also. Bilateral hydrocele was present. The skin over the legs, ankles and feet was cold and firm, and the soles of the feet were red.

Neurologic examination revealed that the pupils reacted to light, in spite of pronounced diminution in visual acuity. Nystagmus on lateral gaze was present. Fundoscopy by an ophthalmologist disclosed slight bilateral optic atrophy, and no cherry red spot of the macula was present. There was no rigidity or hypermotility of the extremities and, except for slight hypoactive deep tendon reflexes, no other abnormality was noted.

Laboratory studies on admission: The urine was normal. A hemogram showed a hemoglobin value of 70 per cent, erythrocytes numbering 4.6 million, and leukocytes 10,200 with 56 per cent lymphocytes, 25 per cent polymorphonuclear cells, 11 per cent eosinophils and 8 per cent monocytes. Results of Kahn, Wassermann and tuberculin tests were negative. The blood cholesterol was 156 mg. per 100 cc.

A pneumoencephalogram was performed. No air entered the subarachnoid space; both lateral ventricles were enlarged, the left more than the right, with a "bat-wing" appearance; the third ventricle was also dilated. A skeletal survey showed the skull and long bones to be normal.

The child remained afebrile throughout the hospital stay of 11 days in spite of a slight upper respiratory infection near the end of the period. Repeated hemograms showed no essential change, although one smear hinted at vacuolization of the lymphocytes and monocytes. The child was discharged with no essential change in status.

Three days later he was readmitted with a flare-up of the eczema and an increase in severity of the respiratory infection. He was acutely ill with a temperature of 102°. The results of physical examination were essentially as before except for changes in the ears and chest. Both tympanic membranes were inflamed and the right chest was flat to percussion and inspiratory and expiratory crepitant rales were heard. An x-ray film of the chest disclosed consolidation in the right lung, and a hemogram revealed leukocytosis.

During the first week the temperature ranged from 102° to 105°. On the seventh day, myringotomy was performed bilaterally, with rapid defervescence. Culture of the pus obtained from the left ear showed staphylococcus aureus and pneumococcus type XXIII. For a week the child appeared much improved, but the fever rose again, with a progressive downhill septic course, and after one month in the hospital, the patient died.

At autopsy the positive findings consisted of emaciation, dehydration and multiple eczematous lesions of the scalp. The right lung was bound to the parietal pleura by dense fibrous adhesions, and some pus pockets were found among them. The liver extended 7.5 cm. below the costal margin,

and the spleen 3 cm. below the left costal border. The heart was hypertrophied and weighed 60 gm. (normal weight for the age, 37 gm.). The right lung showed fibrous tags on the pleural surface and almost complete consolidation. The liver weighed 525 gm. (normal weight, 260 gm.). The surface was smooth, glistening and yellowish brown. The lobular architecture was indistinct. The cut surface was glistening in appearance. The spleen weighed 30 gm. (normal weight, 20 gm.). The surface was purple, smooth and glistening. The pulp scraped readily with a knife. The malpighian bodies were quite prominent. Both kidneys were enlarged, somewhat paler than normal. There was a thrombus in the left renal vein. Bilateral hydrocele was present. The brain weighed 870 gm. (normal weight, 750 gm.). The meningeal vessels were engorged. There was atrophy of the convolutions of the left cerebral hemisphere, particularly in the temporal and parietal regions around the sylvian fissure. The left lateral ventricle was larger than the right and the third ventricle was considerably dilated, measuring 1 cm. in its transverse diameter and 2.5 cm. in the vertical diameter. The cerebellum was not remarkable. Other organs were grossly negative.

Positive microscopic findings included acute bronchopneumonia. In addition, there were large foamy-appearing cells in alveoli and in alveolar walls. The liver parenchyma was displaced by foci of large vacuolated cells. The splenic architecture was obscured by numerous large pale foamy cells (Figure 1). Similar cells were noted in the adrenal cortex. The thymus, lymph nodes, kidneys and sections from the large and small intestine showed infiltrations with foam cells, and the bone marrow was diffusely infiltrated with similar cells (Figure 2). Sections from various portions of the brain showed ganglion cells that were pale, swollen and granular. Some of these were enlarged three to four times normal size; others were slightly larger than normal, but showed definite vacuolization of the cytoplasm and club-like ends. The nuclei, when present, had a tendency to be pushed to one side. Many large foamy cells in which no nuclei could be identified were present. They were usually in the vicinity of the ganglion cells, but it could not be definitely determined whether they represented ganglion cells (Figure 3). There was no inflammatory reaction. The ependyma was not remarkable. The meninges were essentially normal. No evidence of necrosis of any of the cerebral or cerebellar tissue was noted. Smith-Dietrich stains of the foam cells gave a positive reaction. Unfortunately chemical analyses of the organs were not made.

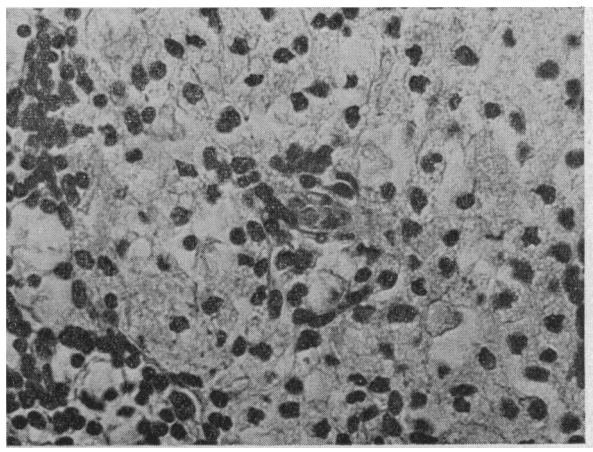

Figure 1.—High power view, spleen, showing large foamy cells.

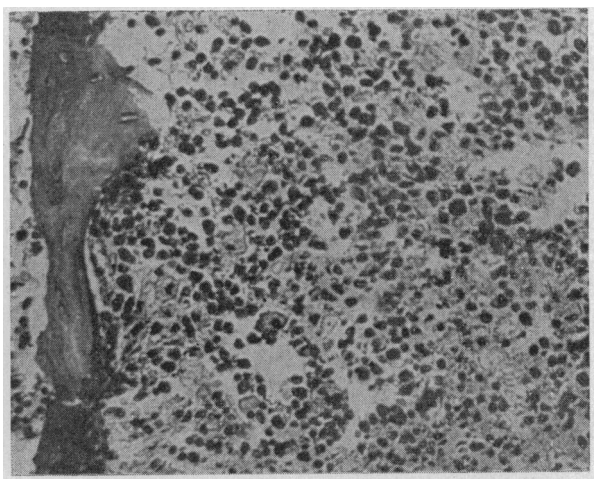

Figure 2.—Bone marrow, sternum, showing almost complete replacement by foam cells.

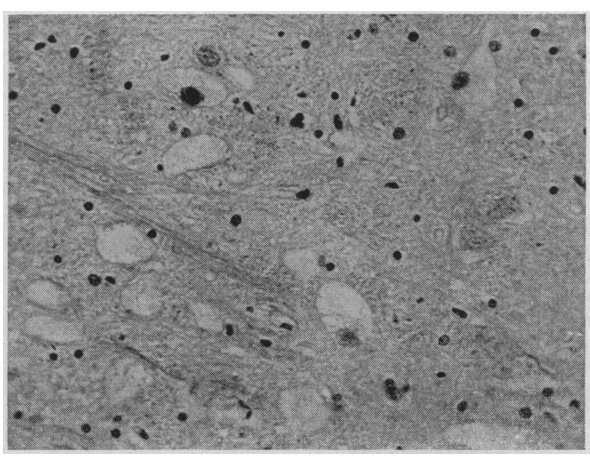

Figure 3.—Medulla, showing swollen foamy ganglion cells, some with foamy granular nuclei.

DISCUSSION

In the case presented there were neurologic signs suggestive of Tav-Sach's disease. This is not a unique finding in Niemann-Pick's disease and has led to considerable speculation concerning a common etiology. In general the points of similarity in the two conditions are: (1) Occurrence in infancy,(2) high incidence in Jews, (3) familial constitutional character, (4) loss of motor and physical functions, (5) lipoidal character of cells in central nervous system, (6) macular degeneration (cherry red spot) in certain cases of Niemann-Pick's disease, (7) absence of macular degeneration in certain cases of Tay-Sach's disease.

Factors against a common pathogenesis in the two diseases are: (1) Involvement of bone marrow, liver, spleen, lymph nodes and other organs as well as the brain in Niemann-Pick's, but not in Tay-Sach's disease, (2) absence of descending degeneration of neurons in Niemann-Pick's disease, (3) differences in lipoid analysis of various organs from the two conditions.

The diagnosis of this group of diseases is dependent upon a correlation of the clinical findings and pathological studies, including chemical analysis. Bone marrow study during life usually points out the lipoid nature of the disease, and frequently suggests the disease in question. Hence it is of great importance. Postmortem examination shows the sites of lip-

oid deposit, and often by means of appropriate staining techniques, a diagnosis is made. Chemical analysis of the organs is of the greatest importance, and it is interesting to note that lipoid fractionations have been done in so few cases. Data derived from this technique will add to knowledge of the mechanism of variations of this class of disorders, and the ultimate diagnosis should depend on such an analysis.

SUMMARY

A case of Niemann-Pick's disease is presented. The findings in the brain closely resembled those described in Tay-Sach's disease. A discussion of the essential lipoid diseases is presented, and the importance of chemical fractionation of the visceral lipoids is stressed.

REFERENCES

1. Canmann: Niemann-Pick's diseases, J. Pediat., 24:335-347, March 1944.

2. Murray, H. A., and Bernstein, T. C.: Niemann-Pick's disease, Arch. Pediat., 63:497-503, Oct. 1946.

3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 1:539, The Williams and Wilkins Company, Baltimore, 1946.

4. Pick, L.: Classification of diseases of lipoid metabolism and Gaucher's disease, Am. J. Med. Sc., 185:453-469, April 1933.

5. Pick, L.: Niemann-Pick's disease and other forms of so-called xanthomatosis (Dunham lecture), Am. J. Med. Sc., 185:601-616, May 1933.

6. Thannhauser, S. J., Benotti, J., and Remstein, H.: Studies on animal lipids: lecithin, cephalin, and sphingomyelin content of normal human organs, J. Biol. Chem., 129:709, Aug. 1939.

7. Thannhauser, S. J.: Lipoidoses, Oxford Medicine, Christian, Vol. IV, Part II, p. 287, Oxford Univ. Press.

8. Thannhauser, S. J., and Magendantz, H.: Different clinical groups of xanthomatous diseases; clinical physiological study of 22 cases, Ann. Int. Med., 11:1662, March 1938.

9. Thannhauser, S. J., and Reichel, M.: J. Biol. Chem., 113:317, 1936.